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REVIEW

Xenotransplantation

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ABSTRACT. The transplantation of living cells, tissues or organs from one species to another is termed xenotransplantation. The history of xenotransplantation is as old as allogeneic transplantation itself. Early attempts were made at a time when the immunologic basis of organ rejection were poorly understood. The advent of potent immunosuppressive medications along with the parallel advances in the field of genetic engineering has provided a fresh perspective on the role of xenotransplantation as a means to alleviate the disparity between the number of candidates on the waitlist and the available organs. As the science behind xenotransplantation advances, the transplantation community must take it upon themselves to educate the community at large regarding both the benefits and potential risks of this promising field.

KEYWORDS. solid organ xenotransplantation, xenograft, xenotransplantation

INTRODUCTION

The ever-increasing number of patients on the transplant list means that there is always going to be a short supply of organs for transplantation, now and in the future, if we continue to rely exclusively on deceased and living donor transplantation from humans. Only around 23,000 to 28,000 organ transplants are being done in the United States among more than 120,000 to 124,000 patients that are on the waiting list.[1,2] In this vacuum, xenotransplantation has posited as a potential game-changer, provided we can cross many hurdles facing it. In contrast to allogeneic transplantation where an organ is transplanted from one individual to another within the same species as is currently widely practiced, in xenotransplantation, an organ is transplanted from one species to another.

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HISTORY

One of the first important studies on xenotransplantation was performed by Reemtsma and colleagues who transplanted chimpanzee kidneys into 13 patients, with survival ranging from 11 days to 9 months.[3–5] Rejection and infection were the main causes behind these early failures, with techniques being continually improved over the decades. Over the years, interest has piqued in pigs due to their ease of domestication and breeding in pathogen-free environments, and relative social acceptance.[1,2,6,7] The pig-to-non human primate as an experimental model is being used extensively to study xenotransplantation today.[8,9]

ADVANCES OVER THE DECADES

Advances in genetic engineering and immunology have reshaped the landscape of xenotransplantation. The ability to genetically modify a pig genome by knocking out the genes that are responsible for producing antigens to which primates form antibodies and the ability to insert human transgenes that provide protection against the immunologic response have been promising, but in itself, have proven unsuccessful in maintaining long term graft survival.[2,10] Efforts to knock out galactose-α1,3-galactose (Gal) which is one of the major carbohydrate antigen on pig vascular endothelial cells to which human recipients have antibodies, and the introduction of human complement-regulatory proteins on pig vascular endothelial cells are examples of some of these efforts that have had varied, short term effects on graft survival.[2,11]

The introduction of clustered regularly interspaced short palindromic repeats (CRISPR) Cas9 technology into the fold has significantly ramped up the pace with which these experiments are being performed.[1,2] Since the discovery of porcine endogenous retroviruses (PERVs) in the pig genome in 1994, efforts have been made to avoid inadvertent transmission of these retroviruses to the recipients as they have the ability to infect recipient cells under stress.[1] The most dramatic of these discoveries has been the successful inactivation of 62 active porcine endogenous retroviruses (PERVs) in a single step by Yang et. al. decreasing the risk of transmission by three orders of magnitude.[12] The CRISPR-Cas9 technology was an unexpected offshoot from basic science research that had focused on bacterial innate immunity against phage that has had tremendous ramifications in the realm of genetic engineering and xenotransplantation.[1]

ADVANTAGES OF XENOTRANSPLANTATION

The obvious advantage of xenotransplantation is the decrease in reliance on human organs. It also serves to counter the unmet need of organ deficit for transplantation worldwide. Besides, patients with high panel reactive antigen (PRA) have shown to be at no higher risk of rejecting a pig graft than patients with low or no PRA based on current limited evidence.[13,14] In addition, certain diseases recur in a rapid fashion leading to kidney failure. Some of these patients may benefit from xenograft, as the possibility of recurrence may be low. In case of living donors, although very safe with modern surgical techniques, there is increasing evidence that living donors, especially certain racial and ethnic groups are at risk for developing chronic kidney disease few decades after donation.[15–18] If xenotransplantation is feasible and successful, it will eliminate living donation for sure.

CURRENT STATUS

The US Food and Drug Administration's (FDA) stance on xenotransplantation has been that it should be limited to "patients with serious or life-threatening diseases for whom adequately safe and effective alternative therapies are not available and who have potential for a clinically significant improvement with increased quality of life following the procedure.[10] Patients who have a high post-transplant probability of mortality when transplanted with an allograft due to their comorbidities or malignant disease may not be good candidates for initial studies on

xenotransplantation as this would not serve as a fair trial of the latter. Instead, subsets of patients with a high degree of allosensitization to human leukocyte antigen (HLA) who have only a miniscule chance of finding a cross-match negative allograft and patients with rapid recurrence of primary disease in previous allografts may be reasonable candidates for pilot studies of xenotransplantation.[10]

FUTURE CHALLENGES

Despite the encouraging results with recent experiments on pigs showing the inactivation of multiple genes encoding for PERVs, there is still a theoretical chance that a retrovirus may be transmitted to the recipient either due to imperfections in the technique that need to be refined further, or due to the limits of our current knowledge regarding the way these genes behave and get transmitted. Should solid organ xenotransplantation come to reality in the future, inevitable comparisons will be made to human allografts and these studies on outcomes are going to be vital in delineating criteria for allo- versus xenotransplantation for future recipients. The societal acceptance (including possible conflicts with religious beliefs and animal rights groups) to the idea of harvesting organs from another species for transplant in humans is something the transplant community will need to address on an ongoing basis.[2] Porcine heart valves, encapsulated pig islet cell transplantation, pig corneal transplantation and bovine vessels have already been used successfully in humans which has had good acceptance in the society in general and solid organ xenotransplantation should be presented to the community in a similar fashion.[2]

CAUTIOUS OPTIMISM

In summary, there are enough reasons to be optimistic that xenotransplantation will completely transform the field of transplantation. The pivotal role of ongoing advances in immunology in developing effective, well tolerated immunosuppressive medications with minimal side effects, and in genetic engineering in further refining current techniques to make the xenograft a safe and viable option for humans cannot be overstated. The transplant community must also bear the responsibility of educating the community and the government oversight agencies of the potentials of xenotransplantation, whilst also tempering unwarranted grandiose reporting of unsubstantiated preliminary studies in mainstream media. Cautious optimism is advised; it took decades after the first kidney transplant in 1954 for it to become a standard of care for patients with renal failure. Xenotransplantation will have to go through its own growing pains as it struggles to find its place in the constantly evolving world of transplantation.

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